



Diet and Other Risk Factors for Laryngeal Cancer in Shanghai, China

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A population-based, case-control study of laryngeal cancer was conducted in Shanghai, China, during 1988–1990, in which 201 incident cases (177 males, 24 females) and 414 controls (269 males, 145 females) were interviewed. Cigarette smoking was the major risk factor, accounting for 86% of the male and 54% of the female cases. After adjusting for smoking, there was little increase in risk associated with drinking alcoholic beverages. Among men, cases more often reported occupational exposures to asbestos and coal dust. A protective effect was associated with the intake of fruits (particularly oranges and tangerines), certain dark green/yellow vegetables, and garlic, but there was an increased risk with the intake of salt-preserved meat and fish. The findings suggest that risk factors for laryngeal cancer in Shanghai resemble those in Western countries, and they provide further evidence that dietary factors play an important etiologic role. *Am J Epidemiol* 1992;136:178–91.

alcohol drinking; ascorbic acid; carotene; case-control studies; diet; laryngeal neoplasms; occupations; tobacco

Cigarette smoking is the major determinant of laryngeal cancer in most areas of the world (1–6). Risk has been shown to increase with the intensity and duration of smoking and to decrease with the years since cessation of smoking. Alcohol drinking has also been linked to laryngeal cancer, and in some studies a multiplicative effect with smoking has been suggested (1–8). In addition, some studies have found that exposure to certain

occupational agents, such as asbestos, may increase the risk of laryngeal cancer (9–13), while others have suggested that a high intake of fruits and vegetables may decrease the risk (14–18). Most investigations of laryngeal cancer have been carried out in Western countries, with none in China, a low-risk area (incidence rate/100,000 men = 3.1 in Shanghai vs. 6.5 among white men in the San Francisco Bay area of California) (19). In this paper, we evaluate the effects of cigarette smoking, alcohol drinking, occupational exposure, and diet in the development of laryngeal cancer, utilizing data from a population-based, case-control study conducted in Shanghai, People's Republic of China, during 1988–1990.

MATERIALS AND METHODS

All residents of urban Shanghai aged 20–75 years who were newly diagnosed with laryngeal cancer during the period from January 1, 1988, to February 28, 1990, were eligible for study. A total of 263 eligible cases were identified from a population-based

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Abbreviation: CI, confidence interval.

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cancer registry in Shanghai during the study
period. This registry, which started opera-
tion in 1963, has essentially complete ascer-
tainment of all cancer cases occurring in the
urban Shanghai area (19). Of the cases iden-
tified, 201 (76.4 percent) were interviewed,
while 62 (23.6 percent) were not included
because of death (51 cases) and inability to
locate (11 cases). Data for pathologic diag-
nosis were collected for the majority (91.5
percent) of cases.

Controls were randomly selected from the
general population of the urban Shanghai
area. The number of controls in each sex-
and age (5-year interval)-specific stratum
was determined in advance according to the
sex and age distributions of the incident
cases of oral, pharyngeal, laryngeal, and na-
sal cancers reported to the Shanghai Cancer
Registry during 1985-1986. The Shanghai
Resident Registry, which keeps personal reg-
istry cards for all adult residents in urban
Shanghai, was used to select controls. For
each sex- and age-predetermined control, a
registry card identifying a potential control
of the same 5-year age group and sex was
randomly selected. A second potential con-
trol was also identified. Of the 414 controls
interviewed, 48 (12 percent) were second
controls. The major reasons for using second
controls were that the first control died be-
fore interviewing (2 percent) or could not be
located (10 percent). No controls or cases
refused to be interviewed.

The cases and controls were interviewed
in person by trained personnel, usually at
the homes of the subjects. A structured ques-
tionnaire was used to elicit detailed infor-
mation on demographic factors, tobacco
smoking, alcohol drinking, dietary habits,
and occupational history and exposures.
Diet was assessed by asking for the "usual
frequency and amount of consumption in
the previous 10-year period, ignoring any
recent changes," of 30 fruits and vegetables
and 11 animal foods, which are the major
foods in the diets of Shanghai residents (see
appendix table). For smoking and drinking
history, the usual amounts of tobacco and
alcoholic beverages consumed in the four

age periods (<20, 20-34, 35-59, and ≥ 60
years) were ascertained. Average intakes of
these two agents were computed by weight-
ing the usual amount and years of consump-
tion across these four age periods. Informa-
tion on supplementary vitamin intake was
also obtained.

The monthly amount (grams) and
monthly frequency of consumption were de-
rived for each food item. For seasonal foods,
the average monthly intake was obtained by
weighting the length of time the food was in
the market in a 1-year interval. Food group
intake was calculated as the sum of the
monthly frequencies or grams of the food
items comprising the food group. Individual
nutrient intake was computed using a
Chinese food composition table (20) and the
amount of food consumed. Consumption of
hard liquor, wine, and beer was converted
into ethanol intake, using the average
ethanol concentration (hard liquor, 53.5
percent; wine, 13.5 percent; beer, 3.9 per-
cent) in these three types of alcoholic bev-
erages (20).

The Mantel-Haenszel stratified estimation
method and unconditional logistic regres-
sion were used to adjust for confounders and
to derive adjusted odds ratios (21). Factors
found to be related to cancer risk in this
study were examined for their potential con-
founding effect on other variables singly and
in combination. After adjustment for age,
smoking, and education, adjustment for
other factors (such as alcohol consumption,
income, exposure to asbestos or coal dust,
and cooking with a kerosene stove) did not
substantially change the odds ratios of laryn-
geal cancer with dietary factors. The strata
used for smoking adjustment were as fol-
lows: <10 pack-years (since only seven cases
and 72 controls never smoked, these subjects
were combined with those who smoked <10
pack-years); 10-29 pack-years; and ≥ 30
pack-years. We tried other methods of
smoking adjustment in data analyses (treat-
ing pack-years as a continuous variable,
grouping pack-years into finer strata, or us-
ing amount and years of smoking), and none
of these alternative adjustments yielded

meaningful differences in the odds ratios. The strata of age and education used for adjustment are specified in table 1. Additional adjustment for dietary factors was not found to significantly change the risk patterns associated with tobacco or alcohol intake. In the diet analysis, food intakes were grouped into categorical variables according to the tertile distribution among controls because no a priori cutpoints or threshold effects had been reported. Since the results based on frequency of consumption were similar to those based on total grams consumed, only the latter results are presented in the paper. Tests for trend across the tertiles were performed in logistic regression by assigning the score j to the j th level of the variable selected. All statistical tests were based on two-tailed probability. The population attributable risk for cigarette smoking was estimated after adjusting for age (22). Since only 24 female cases were included in this study, all detailed analyses were performed for males only. However, a table summarizing major risk factors for females is presented at the end of Results.

RESULTS

The distribution of cases and controls with respect to selected variables is given in table 1. Cases and controls were significantly different in age because of the study design and, thus, age was evaluated as a potential confounder in all analyses. In addition, cases had less education and lower income than controls.

Cigarette smoking was strongly related to laryngeal cancer. The odds ratio was 8.7 (95 percent confidence interval (CI) 3.8–19.6) for ever versus never smoking after adjustment for age and education. Further adjustment for income resulted in little change. The risk increased with increasing daily number of cigarettes and duration of smoking, with 25-fold excesses in the heaviest consumption categories (table 2). Risk declined following cessation of smoking.

Regular alcohol drinkers (drinking alcoholic beverages at least once a week for over 6 months) had a 50 percent excess risk of laryngeal cancer, with odds ratios rising significantly with an increasing amount of

TABLE 1. Distribution of cases and controls by sex, age, education, and income: Shanghai, 1988–1990

Indicators	Males		Females	
	% of cases ($n = 177$)	% of controls ($n = 269$)	% of cases ($n = 24$)	% of controls ($n = 145$)
Age groups (years)*				
<55	10.2	23.1	8.3	25.5
55–59	17.0	12.3	20.8	15.9
60–64	25.4	22.7	37.5	19.3
65–69	29.4	22.7	8.3	15.9
≥70	18.1	19.3	25.0	23.5
Education*				
No formal school	18.1	10.4	58.3	35.9
Primary school	41.2	33.1	20.8	24.1
High school	35.0	43.1	16.7	31.7
College and others	5.7	13.4	4.2	8.3
Income (quartile)†				
Q ₁ ‡ (low)	36.8	21.2	58.3	30.4
Q ₂ ‡	31.0	26.9	29.2	23.2
Q ₃ ‡	17.2	25.8	12.5	23.2
Q ₄ ‡ (high)	14.9	26.2	0	23.2

* $p < 0.01$ for χ^2 test for males.

† $p < 0.01$ for males and females. Three male cases and 23 controls (13 male, 10 female) were deleted because of missing data on income.

‡ Q₁ to Q₄, quartiles 1 to 4, respectively.

TABLE 2. Cigarette smoking and risk of laryngeal cancer among males: Shanghai, 1988-1990

Smoking category	No. of cases	No. of controls	Crude OR*	Adjusted†	
				OR	95% CI*
Never	7	72	1.0	1.0	
Ever	170	197	8.9	8.7	3.8-19.6
Years of smoking‡					
<20	6	44	1.4	1.4	0.4-4.6
20-29	18	42	4.4	4.1	1.6-11.1
30-39	42	33	13.1	12.0	4.8-30.1
≥40	104	78	13.7	13.2	5.6-31.2
Trend test				$p < 0.01$	
Average no. of cigarettes/day‡					
<10	7	48	1.5	1.6	0.5-4.9
10-19	73	103	7.3	7.1	3.1-16.6
20	26	22	12.2	12.4	4.6-33.2
≥20	64	24	27.4	25.1	9.9-63.2
Trend test				$p < 0.01$	
Pack-years‡					
<10	6	42	1.4	1.4	0.4-4.5
10-19	15	50	3.1	2.9	1.1-7.9
20-29	13	39	3.4	3.1	1.1-8.6
30-39	39	26	15.4	15.4	6.0-39.6
≥40	97	40	25.1	25.1	10.3-61.2
Trend test				$p < 0.01$	
Years since quitting smoking					
<2 or current smokers§	135	150	1.0	1.0	
2-4	13	7	2.1	1.8	0.6-4.9
5-9	8	14	0.6	0.6	0.2-1.5
≥10	14	26	0.6	0.6	0.3-1.2
Nonsmokers	7	72	0.1	0.1	0.0-0.2

* OR, odds ratio; CI, confidence interval.

† Adjusted for age and education.

‡ Odds ratios were compared with those of nonsmokers.

§ Reference category.

tion of cases and controls with adjusted variables is given in table 2. Controls were significantly different because of the study design was evaluated as a potential confounder. In addition, cases had higher education and lower income than

controls. Smoking was strongly related to laryngeal cancer. The odds ratio was 8.7 (95 percent confidence interval (CI) 3.8-19.6) for ever smoking after adjustment for education. Further adjustment for age resulted in little change. The odds ratio increased with increasing daily cigarette consumption and duration of smoking. The risk was highest in the heaviest smoking categories (table 2). Risk decreased with cessation of smoking. Alcohol drinkers (drinking alcohol at least once a week for over 5 years) had a 50 percent excess risk of laryngeal cancer, with odds ratios rising significantly with an increasing amount of

Income: Shanghai, 1988-1990

Females	
% of cases (n = 24)	% of controls (n = 145)
8.3	25.5
20.8	15.9
37.5	19.3
8.3	15.9
25.0	23.5
58.3	35.9
20.8	24.1
16.7	31.7
4.2	8.3
58.3	30.4
29.2	23.2
12.5	23.2
0	23.2

) were deleted because of missing data

weekly or lifetime ethanol intake, lifetime hard liquor consumption, and years of ethanol use (table 3). Such a dose-response relation persisted after adjusting for age and education, but disappeared after additionally adjusting for smoking. No significant relation was found with lifetime consumption of wine and beer, but the consumption level was low.

A strong correlation was found between cigarette smoking and alcohol consumption (Pearson's correlation coefficient = 0.46 for pack-years of cigarette and lifetime ethanol intake among controls). As shown in table

4, the odds ratios rose sharply with increasing pack-years in each consumption level of alcohol. In contrast, the odds ratios tended to increase only slightly with increasing intake of alcohol in each smoking category, although there was a surprisingly high odds ratio of 35.7 (95 percent CI 13.6-93.9) among heavy smokers who did not drink. After adjusting for smoking, there was no excess risk in heavy drinkers compared with nondrinkers.

Since occupation was highly correlated with education, only smoking and age were adjusted for in the analysis of occupational

TABLE 3. Alcohol consumption and risk of laryngeal cancer among males: Shanghai, 1988-1990

Drinking category	No. of cases	No. of controls	Crude OR*	Adjusted†	
				OR	95% CI*
Never	80	149	1.0	1.0	
Ever	97	120	1.5	0.8	0.6-1.4
Years of drinking‡					
<20	14	38	0.7	0.7	0.3-1.5
20-29	13	20	1.2	0.9	0.4-2.3
30-39	17	17	1.9	1.1	0.4-2.7
≥40	53	45	2.2	0.9	0.5-1.6
Weekly ethanol intake (g)‡, §					
<144	16	31	1.0	0.8	0.4-1.7
144-284	22	30	1.4	1.0	0.5-2.0
285-479	27	29	1.7	0.9	0.5-1.9
≥480	32	30	2.0	0.8	0.4-1.6
Lifetime ethanol intake (kg)‡, §					
<135	12	30	0.7	0.8	0.3-1.9
135-383	14	30	0.9	0.5	0.2-1.2
384-827	30	30	1.9	1.3	0.6-2.6
≥828	41	30	2.5	0.9	0.5-1.7
Lifetime hard liquor intake (kg)‡,					
<405	16	29	1.0	0.8	0.3-1.7
405-1,224	26	29	1.7	1.1	0.5-2.2
≥1,225	39	28	2.6	0.8	0.4-1.6

* OR, odds ratio; CI, confidence interval.

† Adjusted for age, education, and smoking.

‡ Odds ratios were compared with those of nondrinkers.

§ Subjects were grouped according to quartile levels of drinking controls.

|| Subjects were grouped according to tertile levels of controls who drank hard liquor. Subjects who ever drank, but did not drink hard liquor, were excluded in the analysis.

factors. Using professional and administrative workers as the reference, no job category showed a significantly elevated risk after adjusting for smoking (table 5). A twofold excess risk was observed among drivers and other transportation workers; within this group, eight cases versus one control were sailors. No significantly elevated risk was found among any of the eight industry categories in which the subjects worked for most of their lives.

Self-reported occupational exposure to coal dust was associated with a significantly increased risk of laryngeal cancer, with an odds ratio of 2.6 (95 percent CI 1.4-4.8) after adjusting for age, education, and smoking. The risk increased with frequency and duration of exposure, with odds ratios of 3.7 (95 percent CI 1.8-7.6) for daily exposure and 3.4 (95 percent CI 1.2-9.4) for 10 or

more years of exposure to coal dust. An elevated odds ratio was associated with asbestos exposure (odds ratio = 2.0, 95 percent CI 1.0-4.3), although no dose-response relation with frequency or duration of exposure was observed.

Dietary analyses revealed an elevated risk associated with increasing consumption of salt-preserved meat and fish, which remained after adjustment for smoking and education, but use of these foods was infrequent (table 6). No relation was seen with salt-preserved vegetables, and the relation with salt-preserved eggs disappeared after adjustment for salted meat/fish intake, with adjusted odds ratios of 1.0, 0.9, 1.2, and 1.0 with increasing frequency of intake of salted eggs. The dose-response relation for salted meat/fish remained significant after additional adjustment for salted eggs and vege-

Shanghai, 1988-1990

Age (yr)*	Adjusted†	
	OR	95% CI*
0	1.0	
5	0.8	0.6-1.4
7	0.7	0.3-1.5
2	0.9	0.4-2.3
9	1.1	0.4-2.7
2	0.9	0.5-1.6
0	0.8	0.4-1.7
4	1.0	0.5-2.0
7	0.9	0.5-1.9
0	0.8	0.4-1.6
7	0.8	0.3-1.9
9	0.5	0.2-1.2
9	1.3	0.6-2.6
5	0.9	0.5-1.7
0	0.8	0.3-1.7
7	1.1	0.5-2.2
6	0.8	0.4-1.6

Subjects who ever drank, but did not drink

exposure to coal dust. An association was associated with age (odds ratio = 2.0, 95 percent confidence interval 1.0-4.0), although no dose-response relationship or duration of exposure was observed.

Analyses revealed an elevated risk of laryngeal cancer with increasing consumption of meat and fish, which remained after adjustment for smoking and duration of exposure. Use of these foods was infrequent.

No relation was seen with consumption of vegetables, and the relation between consumption of salted eggs disappeared after adjustment for salted meat/fish intake, with odds ratios of 1.0, 0.9, 1.2, and 1.0 for frequency of intake of salted meat, white meat, and fresh fish were not related to cancer risk. Consumption of liver, however, was associated with an increased risk, with an odds ratio of 2.2 (95 percent confidence interval 1.0-3.2) in the highest intake group, but intake in general was low.

TABLE 4. Odds ratios of laryngeal cancer by tobacco and alcohol consumption among males: Shanghai, 1988-1990

Pack-years	Lifetime ethanol intake											
	0 kg			<300 kg			300-899 kg			≥900 kg		
	No.	OR*	95% CI*	No.	OR†	95% CI	No.	OR†	95% CI	No.	OR†	95% CI
0-9												
Controls	84			21			5			4		
Cases	7	1.0	Ref.*	2	1.0	0.2-5.5	3	7.5	1.4-38.8	1	2.5	0.2-27.0
10-29												
Controls	44			20			22			3		
Cases	12	3.1	1.1-8.7	7	3.8	1.1-12.1	7	3.7	1.1-12.0	2	7.4	1.0-55.0
≥30												
Controls	21			12			16			17		
Cases	61	35.7	13.6-93.9	12	12.1	3.8-38.6	31	23.2	8.3-65.0	32	25.1	9.6-70.0
Total												
Controls	149			53			43			24		
Cases	80	1.0	Ref.	21	0.6§	0.3-1.3	41	1.0§	0.6-1.9	35	1.0§	0.5-2.0

* OR, odds ratio; CI, confidence interval; Ref., reference.

† Adjusted for age and education.

‡ Further adjusted for alcohol consumption.

§ Further adjusted for smoking.

tables. Risk was elevated with frequent consumption of deep-fried foods, but no clear dose-response relation was observed.

Fruits and vegetables were grouped according to their botanical similarity and nutrient content (see appendix table). As shown in table 7, reduced risks of laryngeal cancer were found with increased consumption of most fruit and vegetable subgroups, with especially pronounced effects for dark green vegetables (other than bok choy), dark yellow vegetables, garlic, and oranges/tangerines. Additional adjustment for salt-preserved meat/fish generally decreased the odds ratios for the heaviest consumption level of these foods even further. Bok choy was considered separately from other dark green vegetables because, in contrast to other dark green vegetables, bok choy has a heavy, white to light green stem. Bok choy accounts for 22 percent of the total vegetable and 54 percent of the dark green vegetable intake in Shanghai. When the other dark green vegetables were considered, significant inverse trends were found for intake of spinach, green and red peppers, and snow peas. Red meat, white meat, and fresh fish were not related to cancer risk. Consumption of liver, however, was associated with an increased risk, with an odds ratio of 2.2 (95 percent confidence interval 1.0-3.2) in the highest intake group, but intake in general was low.

Analyses were also performed for other individual foods. Significantly reduced risks of laryngeal cancer were related to carrot intake, with odds ratios of 1.0, 0.6, and 0.4, respectively, for low to high consumption (trend test, $p = 0.03$). The white radish, the most common vegetable likely eaten raw in Shanghai, was significantly associated with a reduced risk (trend test, $p < 0.01$). An inverse relation between lettuce and cancer risk was also observed, although it was not statistically significant (trend test, $p = 0.07$). There were nonsignificant 20 percent decreases in risk for each of the highest consumption tertiles of the three cruciferous vegetables we asked about. Reduced risks were associated with a variety of individual fruits, such as apples, pears, peaches, bananas, and watermelon, although trends were less pronounced than that for oranges/tangerines.

Since dark green/yellow vegetables (other than bok choy), oranges/tangerines, and garlic contributed different nutrients, and since the correlation coefficients among them were low (<0.20), we included them simultaneously in one logistic regression to examine their independent effects. Dark

Since dark green/yellow vegetables (other than bok choy), oranges/tangerines, and garlic contributed different nutrients, and since the correlation coefficients among them were low (<0.20), we included them simultaneously in one logistic regression to examine their independent effects. Dark

TABLE 5. Usual occupations and occupational exposures and risk of laryngeal cancer among males: Shanghai, 1988-1990

Occupation categories	No. of cases	No. of controls	OR*, †	OR‡	95% CI*, ‡
Professional and administrative workers	47	92	1.0§	1.0§	
Commercial workers	14	15	1.9	2.0	0.7-5.6
Service workers	14	29	0.9	0.6	0.3-1.5
Farmers	4	8	0.9	0.7	0.2-3.0
Metal refining and processing workers	10	15	1.2	1.2	0.4-2.3
Chemical, rubber, and leather workers	6	11	1.0	1.1	0.3-3.6
Textile workers	9	7	2.2	1.7	0.5-6.0
Blacksmiths, machine-tool operators, electricians, and other related workers	12	25	1.0	1.2	0.5-3.1
Material handling and construction workers	19	14	2.5	1.4	0.6-3.5
Drivers and other transportation workers	22	12	3.8	2.3	0.9-5.6
Other workers	20	41	1.1	1.1	0.5-2.5
Occupational exposure					
Asbestos	26	22	1.9	2.0	1.0-4.3
Silica	47	52	1.4	1.3	0.8-2.3
Coal dust	38	32	1.8	2.6	1.4-4.8
Wood dust	17	20	1.3	1.4	0.6-3.2
Metal dust	49	62	1.2	1.2	0.7-2.0
Benzene	24	39	1.0	1.0	0.5-1.9
Paint	29	38	1.1	1.1	0.6-2.1
Pitch	14	13	1.3	1.3	0.5-3.2
Diesel/gasoline/kerosene fumes	49	75	1.1	1.0	0.6-1.7
Lubricant fumes	25	51	0.8	0.8	0.4-1.5
Hydrochloric acid	17	30	0.8	0.8	0.4-1.6

* OR, odds ratio; CI, confidence interval.

† Adjusted for age.

‡ Further adjusted for smoking.

§ Reference category.

|| Further adjusted for education.

green and yellow vegetables were combined into one group because both are major contributors of β -carotene and other carotenoids. The multivariate model showed that the protective effects of dark green/yellow vegetables and oranges/tangerines persisted, while an inverse association with garlic remained but was no longer statistically significant. The results remained unchanged after additional adjustment for tomato and cruciferous vegetable intake.

The effects of specific micronutrients are shown in table 8. Risks were reduced with the estimated higher intake of carotene and vitamin C, although the lowest odds ratios were observed among those in the middle

third of intake and the trends were not statistically significant.

To investigate the possible interactive effect of cigarette smoking and dietary factors in the development of laryngeal cancer, we examined the influence of selected foods and nutrients at three levels of cigarette smoking (table 9). Because of the small number of cases in the highest tertile of intake among those smoking less than 10 pack-years, the upper two tertiles for each variable were combined. Risks consistently increased with decreasing intake of dark green/yellow vegetables, oranges/tangerines, and estimated carotene in each stratum of cigarette smoking.

Laryngeal cancer among males:

No. †	OR‡	95% CI*, ‡
15	1.0§	
1	2.0	0.7-5.6
1	0.6	0.3-1.5
1	0.7	0.2-3.0
1	1.2	0.4-2.3
1	1.1	0.3-3.6
1	1.7	0.5-6.0
1	1.2	0.5-3.1
1	1.4	0.6-3.5
2	2.3	0.9-5.6
1	1.1	0.5-2.5
2	2.0	1.0-4.3
1	1.3	0.8-2.3
2	2.6	1.4-4.8
1	1.4	0.6-3.2
1	1.2	0.7-2.0
1	1.0	0.5-1.9
1	1.1	0.6-2.1
1	1.3	0.5-3.2
1	1.0	0.6-1.7
1	0.8	0.4-1.5
1	0.8	0.4-1.6

TABLE 6. Consumption of salt-preserved or deep-fried foods and risk of laryngeal cancer among males: Shanghai, 1988-1990

Frequency of consumption	No. of cases	No. of controls	Crude OR*	Adjusted†	
				OR	95% CI*
Salt-preserved vegetables					
Never/occasionally	82	156	1.0	1.0	
Monthly	22	14	3.0	2.9	1.2-6.8
Weekly	44	56	1.5	1.5	0.8-2.6
Daily	28	42	1.3	1.1	0.6-2.2
Trend test				$p = 0.38$	
Salt-preserved eggs					
Never/occasionally	73	154	1.0	1.0	
Monthly	27	38	1.5	1.2	0.6-2.4
Weekly	59	61	2.0	1.8	1.1-3.1
Daily	18	15	2.5	1.7	0.7-4.0
Trend test				$p = 0.03$	
Salt-preserved meat/fish					
Never/occasionally	109	229	1.0	1.0	
Monthly	32	24	2.8	2.7	1.4-5.3
Weekly	33	11	5.0	4.3	2.0-9.2
Daily	3	4			
Trend test				$p < 0.01$	
Deep-fried foods					
Never/occasionally	69	180	1.0	1.0	
Monthly	28	26	2.8	3.5	1.7-7.5
Weekly	63	49	3.4	3.6	2.1-6.4
Daily	16	13	3.2	2.5	1.0-6.1
Trend test				$p < 0.01$	

* OR, odds ratio; CI, confidence interval.

† Adjusted for age, education, and smoking.

and the trends were not significant.

the possible interactive effects of smoking and dietary factors in the development of laryngeal cancer, we examined the influence of selected foods and the levels of cigarette smoking. Because of the small number of cases in the lowest tertile of intake among men with less than 10 pack-years, the odds ratios for each variable were not consistently increased with increasing intake of dark green/yellow vegetables, tangerines, and estimated stratum of cigarette smoking.

Only 15 cases and 27 controls reported ever taking vitamin pills at least once a week for 2 or more months 2 years prior to the diagnosis (for cases) or interview (for controls). The adjusted odds ratio among pill users was 1.3 (95 percent CI 0.6-2.9). No data were available on reasons for intake of the vitamin pill, i.e., whether it was being used as a dietary supplement for healthy people or as a treatment for illness.

Table 10 summarizes the major risk factors for laryngeal cancer among women. Cigarette smoking was strongly related to risk, with odds ratios of 9.4 and 20.2 for women with less than 10 and 10 or more pack-years, respectively. The population attributable risk for smoking was 54 percent (95 percent CI 32-76). Alcohol drinking imparted an

elevated risk (odds ratio = 4.8), but only five cases and four controls were drinkers. High intakes of salt-preserved meat/fish and of deep-fried foods were associated with increased risk, while high intakes of dark yellow vegetables, garlic, and fruits were linked to decreased risk. Although the odds ratios among women were not statistically significant because of small sample size, the results were generally similar to those observed among males.

DISCUSSION

Cigarette smoking was the main risk factor for laryngeal cancer in this study in Shanghai, consistent with previous epidemiologic studies, mainly in Western coun-

TABLE 7. Intake of selected food items and risk of laryngeal cancer among males: Shanghai, 1988-1990

	Odds ratio* (tertile)†			p value for trend
	T ₁ ‡ (low)	T ₂ ‡	T ₃ ‡ (high)	
Vegetables				
Total	1.0	0.6	1.2	0.61
Dark green	1.0	0.7	0.8	0.39
Bok choy	1.0	0.8	1.2	0.63
Other dark green	1.0	0.4	0.3	<0.01
Dark yellow§	1.0	0.6	0.6	0.08
Tomatoes	1.0	0.9	1.2	0.45
Raw	1.0	0.6	0.8	0.29
Cruciferous	1.0	0.6	0.7	0.21
Legumes	1.0	0.6	0.9	0.75
Garlic§	1.0	0.6	0.5	0.02
Fruits				
Total	1.0	0.6	0.7	0.21
Oranges and tangerines	1.0	0.5	0.4	<0.01
Others	1.0	0.5	0.9	0.44
Animal foods				
Red meat	1.0	0.8	1.3	0.32
White meat	1.0	0.9	1.3	0.37
Fresh fish	1.0	1.0	0.8	0.31
Liver§	1.0	1.3	2.2	<0.01

* Adjusted for age, education, and smoking.

† Unless otherwise noted, subjects were categorized according to the closest tertile level of controls.

‡ T₁ to T₃, tertiles 1 to 3, respectively.§ The lowest levels for dark yellow vegetables, garlic, and liver referred to those who never or occasionally ate these foods (43%, 51%, and 72% of the controls, respectively). The T₂/T₃ cutpoints were the 70th percentile for dark yellow vegetables and the 90th percentile for garlic and liver.

TABLE 8. Odds ratios of laryngeal cancer associated with dietary intake of nutrients among males: Shanghai, 1988-1990

Nutrients (mg)*	No. of cases	No. of controls	Adjusted†	
			OR‡	95% CI‡
Carotene				
<2.1	84	90	1.0	
2.1-3.3	36	91	0.4	0.3-0.8
≥3.4	57	90	0.8	0.5-1.3
Trend test			p = 0.28	
Vitamin C				
<136.4	78	90	1.0	
136.4-204.9	42	91	0.6	0.3-1.1
≥205.0	57	90	0.8	0.5-1.4
Trend test			p = 0.38	

* Subjects were grouped according to tertile levels of controls.

† Adjusted for age, education, and smoking.

‡ OR, odds ratio; CI, confidence interval.

tries (1-6). The risks increased with both intensity and duration of smoking and declined following cessation. An effect of alcohol drinking was evident mainly among

women, although few were drinkers, while little excess risk was detected among men who were heavy drinkers once smoking was controlled for. Such a weak association with

ng males: Shanghai, 1988-1990

T ₃ † (high)	p value for trend
1.2	0.61
0.8	0.39
1.2	0.63
0.3	<0.01
0.6	0.08
1.2	0.45
0.8	0.29
0.7	0.21
0.9	0.75
0.5	0.02
0.7	0.21
0.4	<0.01
0.9	0.44
1.3	0.32
1.3	0.37
0.8	0.31
2.2	<0.01

vel of controls.

io never or occasionally ate these foods
centile for dark yellow vegetables and the

of nutrients among males:

Adjusted†	
R†	95% CI†
.0	
.4	0.3-0.8
.8	0.5-1.3
0.28	
.0	
.6	0.3-1.1
.8	0.5-1.4
0.38	

gh few were drinkers, while
k was detected among men
y drinkers once smoking was
Such a weak association with

TABLE 9. Odds ratios of laryngeal cancer by consumption level of selected foods and cigarette smoking among males: Shanghai, 1988-1990

Food and nutrient items*	Tobacco consumption (pack-years)								
	<10			10-29			≥30		
	No. of cases	No. of controls	OR†	No. of cases	No. of controls	OR†	No. of cases	No. of controls	OR†
Dark green/yellow vegetables									
T ₃ /T ₂ ‡	5	76	1.0§	11	59	2.8	78	44	30.8
T ₁ (low)	8	38	3.7	17	30	8.9	58	22	43.8
Oranges and tangerines									
T ₃ /T ₂	8	85	1.0§	15	59	2.7	60	41	16.6
T ₁ (low)	5	29	2.0	13	30	4.3	76	25	36.9
Total carotene									
T ₃ /T ₂	8	77	1.0§	14	63	2.1	71	41	18.5
T ₁ (low)	5	39	1.3	14	26	5.4	65	25	26.9

* Cases and controls were categorized according to the closest tertile level of controls.

† Odds ratio (OR) adjusted for age and education.

‡ T₁ to T₃, tertiles 1 to 3, respectively.

§ Reference group.

|| Ninety-five percent confidence interval did not include 1.

alcohol consumption may be due to the characteristic behavior of drinking alcohol usually along with foods, thus perhaps diluting the effects of the alcohol. Detailed occupational analyses were not possible because of the relatively small sample size, but we observed excess risks associated with occupational exposure to asbestos and coal dust, as suggested in previous studies (9-13). These findings indicate that the key to the prevention of laryngeal cancer in Shanghai is the reduction of the prevalence and amount of smoking, while suggesting that some occupational exposures contribute to the risk. In addition, our search for dietary risk factors, which have received only limited attention in previous studies of laryngeal cancer, was revealing and warrants further investigation.

The risk of laryngeal cancer was inversely associated with dark green and yellow vegetables, citrus fruits, and garlic. Although many studies have indicated that a high intake of fruits and vegetables may decrease the risk of lung cancer (23), only a few have reported such an effect for laryngeal cancer. The earliest was a hospital-based, case-control study in New York, which linked a high intake of vitamins A and C to a decreased risk of laryngeal cancer (14). Case-

control studies in India (15), Uruguay (16), and Italy (18) revealed two- to threefold excess risks among subjects with infrequent intake of fruits and vegetables. In Texas, a protective effect of carotene was also observed, with an elevated odds ratio of 2.1 for the lowest tertile of intake (17). The mechanisms are unclear, but fruits and vegetables contain vitamin C, β -carotene, and other carotenoids, which are efficient antioxidants and can prevent damage to chromosomes, enzymes, and cell membranes caused by the peroxidation of free radicals (24). In addition, vitamin C can block the endogenous formation of *N*-nitroso compounds (25), which are strong carcinogens in animal models and are suspected to cause certain cancers in humans (26).

Although β -carotene may explain the inverse association of laryngeal cancer with intake of dark green/yellow vegetables (27), other constituents, however, may be involved as well. Dark green vegetables are rich also in oxygenated carotenoids or xanthophylls, primarily lutein and its stereoisomers (27). In contrast to many Western countries, one of the major carotenoids in the Shanghai diet is lutein (J. T. Tu, Shanghai Cancer Institute, personal communication, 1991), which (unlike β -carotene) is not

TABLE 10. Cigarette smoking, alcohol consumption, and dietary factors and risk of laryngeal cancer among females: Shanghai, 1988-1990

Exposure variables	No. of cases	No. of controls	Crude OR*	Adjusted	
				OR	95% CI*
Cigarette smoking (pack-years)†					
0	10	132	1.0	1.0	
1-9	5	7	9.4	9.4	2.4-37.2
≥10	9	6	19.8	20.2	5.3-76.9
Regular alcoholic beverage drinking‡					
No	19	141	1.0	1.0	
Yes	5	4	9.3	4.8	0.8-28.3
Consumption of salt-preserved meat/fish‡					
Never/occasionally	17	118	1.0	1.0	
Often	7	27	1.8	2.3	0.7-7.6
Consumption of deep-fried food‡					
Never/occasionally	13	99	1.0	1.0	
Often	11	46	1.8	2.2	0.8-6.6
High intake of the following food items§					
All vegetables	13	72	1.2	1.1	0.4-3.2
Dark green (except bok choy)	10	66	0.9	0.9	0.3-2.6
Dark yellow	9	72	0.6	0.5	0.2-1.3
Tomatoes	10	68	0.8	1.1	0.4-3.1
Raw	12	72	1.0	1.0	0.4-2.7
Cruciferous	14	64	1.8	3.0	1.0-9.2
Garlic	6	45	0.7	0.7	0.2-2.1
All fruits	9	72	0.6	0.5	0.2-1.5
Oranges/tangerines	8	55	0.8	0.7	0.2-2.1
Liver	9	38	1.7	1.9	0.6-5.6

* OR, odds ratio; CI, confidence interval.

† Adjusted for age (<60, ≥60 years old), education (no formal schooling, primary school or higher).

‡ Adjusted for age, education, and smoking (ever, never). "Often" referred to having eaten the indicated food monthly or more often.

§ Adjusted for age, education, and smoking. Subjects were categorized according to the median level of the selected foods among controls.

a vitamin A precursor (28). Since reliable data were not available on the amount of individual carotenoids in fruits and vegetables, we derived only approximate estimates of carotene intake, which includes several major carotenoids in fruits and vegetables (23). An inverse but nonsignificant association with laryngeal cancer risk was observed with this mixed carotene index; however, the protective effect was weaker than that noted with dark green/yellow vegetables or fruits. It is possible that protective effects derive mainly from specific carotenoids (e.g., β -carotene) but not others.

A protective effect of vitamin C was suggested in this study by the inverse association

of laryngeal cancer with intake of oranges/tangerines. An estimate of dietary vitamin C, however, was not found to be significantly related to laryngeal cancer despite an overall inverse association. Our analysis was limited by an imprecise estimate of vitamin C from vegetables, which are usually eaten cooked (which diminishes the content of vitamin C), while we computed vitamin C based on the food composition of raw vegetables.

We could not derive dietary retinol intake in this study because amounts are available in the Chinese food composition table only for liver, eggs, and milk. However, we did not find a protective effect from high consumption of these retinol-rich foods. In con-

Adjusted risk of laryngeal cancer

	Adjusted	
	OR	95% CI*
0	1.0	
1.4	9.4	2.4-37.2
1.8	20.2	5.3-76.9
0	1.0	
1.3	4.8	0.8-28.3
0	1.0	
0.8	2.3	0.7-7.6
0	1.0	
0.8	2.2	0.8-6.6
0.2	1.1	0.4-3.2
0.9	0.9	0.3-2.6
0.6	0.5	0.2-1.3
0.8	1.1	0.4-3.1
0	1.0	0.4-2.7
0.8	3.0	1.0-9.2
0.7	0.7	0.2-2.1
0.6	0.5	0.2-1.5
0.8	0.7	0.2-2.1
0.7	1.9	0.6-5.6

or higher).
 *ten the indicated food monthly or more
 the median level of the selected foods

cancer with intake of oranges/estimate of dietary vitamin C was not found to be significantly increased despite an overall trend. Our analysis was limited by the estimate of vitamin C from food which are usually eaten cooked and the content of vitamin C in the imputed vitamin C based on the composition of raw vegetables. We derived dietary retinol intake from the use of amounts available in the food composition table only and milk. However, we did not observe a protective effect from high consumption of retinol-rich foods. In con-

trast, a positive association between laryngeal cancer risk and liver consumption was observed. Although this finding may be due to chance alone because of multiple comparisons, it is consistent with the positive relations reported between a high intake of liver and risks of esophageal cancer (29-31) and oral cancer (32), which have risk factor profiles somewhat similar to that of laryngeal cancer.

Little published evidence is available on possible interactions between cigarette smoking and dietary factors in the risk of laryngeal cancer. One study suggested that smoking and low fruit intake combine in a more-than-additive fashion to increase laryngeal cancer risk (16), while another suggested that the protective effect of carotene was mainly among those who stopped smoking 2-10 years ago (17). Our data suggest independent effects of smoking and dietary factors, perhaps combining in a more-than-additive fashion, but power to discriminate between alternative interactive models was not high.

An unexpected finding of our study was the relation of laryngeal cancer risk to intake of salt-preserved meat/fish. The lack of association with salt-preserved vegetables argues against the possible role of recall or interview bias. Although salt and salt-preserved foods are considered risk factors for stomach cancer (33) and perhaps esophageal cancer (33), a relation to laryngeal cancer has not previously been reported. It is noteworthy that several studies in Chinese populations implicated salted fish in the high risk of nasopharyngeal cancer (34-38). *N*-Nitroso compounds have been suggested to play a role in the salted foods linked to nasopharyngeal and gastric cancers in China (26), but other agents such as bacterial and fungal toxins may be involved as well.

A significantly reduced risk of laryngeal cancer was observed in relation to intake of garlic. Although some studies have shown that garlic or certain components in garlic can reduce the rate of a variety of tumors in experimental animals (39-41), limited information is available in humans. To date, only gastric cancer has been inversely related to

garlic intake (42-44). Garlic and other allium vegetables may reduce the conversion of nitrates to nitrites and decrease the endogenous formation of *N*-nitroso compounds by retarding bacterial growth in the gastric cavity, and they may possess other properties that could inhibit the risk of laryngeal and other tumors (39-41).

Some methodological aspects of this study may have influenced our results. First, we collected information on the usual adult diet in the past 10 years, ignoring any recent changes. Several studies have shown that recall of past diet can be influenced by current diet (45). Many cancers, including laryngeal cancer, may interfere with the patient's ability to eat and sharply change current dietary patterns, although there is no reason to suspect that the patients would, because of illness, eat more salt-preserved meat/fish but less vegetables and fruits, especially soft fruit such as oranges and tangerines. A residual confounding effect of smoking needs to be considered because smoking is the dominant risk factor for laryngeal cancer and because smokers tend to consume less dark yellow or cruciferous vegetables and oranges/tangerines in this study. Nonadjustment or inadequate adjustment of smoking may result in a false inverse association between laryngeal cancer and intake of certain fruits and vegetables. However, we adjusted for smoking in several ways with increasingly finer stratification and found little change in the odds ratios for the major dietary and other variables, so that residual confounding is unlikely to be substantial.

In summary, this case-control study of laryngeal cancer in Shanghai, the first one conducted in a Chinese population with a low incidence rate, indicated that cigarette smoking is the most important risk factor. Smoking accounted, at least in part, for 86 percent of the male and 54 percent of the female cases in this population. Alcohol consumption was shown to be a relatively weak risk factor, while occupational exposures to asbestos and coal dust appear to contribute to some cases among men. High intake of fruits and vegetables, especially certain dark yellow and green vegetables, garlic, and or-

anges and tangerines, was shown to be inversely associated with risk, consistent with the protective effects of β -carotene, vitamin C, other micronutrients, and/or food constituents concentrated in vegetables and fruits. In addition, the risk of laryngeal cancer showed a positive association with the consumption of salt-preserved meat and fish, perhaps because of the content of *N*-nitroso compounds. This study, together with previous epidemiologic and experimental studies, indicates that dietary factors may play an important role in the etiology of laryngeal cancer.

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APPENDIX TABLE 1. Food items in the diet section of the questionnaire: Shanghai, 1988-1990

Animal foods	Vegetables	Fruits
Pork, back portion	Dark green	Oranges/tangerines
Pork, spareribs	Bok choy	Apples
Pork, lean	Spinach	Pears/peaches
Liver	Green/red pepper	Watermelons
Beef	Snow peas	Bananas
Poultry meat	Spring onion/chive	
Eggs	Dark yellow	
Fresh fish	Carrots	
Yellow eel	Sweet potatoes	
Fresh cow's milk	Raw	
Powdered cow's milk	White radishes	
	Lettuce	
	Cucumbers	
	Cruciferous	
	Cabbage	
	Chinese cabbage	
	Cauliflower	
	Legumes	
	Peas	
	Snow bean	
	Green/string bean	
	Green broad bean	
	Others	
	Garlic	
	Celery	
	Bean sprouts	
	Eggplant	
	Wild rice stem	
	Potato	
	Wax gourd/okra	
	Tomatoes	
	Bean curd	